PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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10/9/03

Applicants: Batra et al.	)	
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Serial No.: 09/894,921	)	Examiner: Sharareh, Shahnam J.
	)	
Docket No.: 20243CA	)	
	)	Art Unit: 1617
Filed: June 28, 2001	)	
	)	
For: "COMPRESSED TABLET FORMULATION"	)	

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE ACCOMPANYING REQUEST FOR CONTINUED EXAMINATION

Sir:

This communication is being submitted with and forms part of a Request for Continued Examination (RCE) and is a response to the Office Action mailed June 4, 2003, which set a three-month period for response that expired on September 4, 2003. Accompanying this communication is a petition under 37 C.F.R. § 1.136 for a one-month extension of time to October 4, 2003.

Claims 1-16 and 24-44 are pending. None of the claims is amended herein. Reconsideration of the subject application is requested.

Claims 1-16 and 24-44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Makooi (US 6,238,695 B1) in view of Remington: The Science and Practice of Pharmacy, 19th edition, pp. 1616-1620 ("Remington") and US 5,874,430 ("Christ"). This rejection is

traversed with respect to all claims.

The Examiner has acknowledged that Makooi teaches efavirenz capsules and tablets that contain 10 wt.% or more of a superdisintegrant, whereas the instantly claimed compressed tablet contains only 1-5 wt.% superdisintegrant. However, the Examiner has further asserted that Makooi nowhere "suggests that a low level of superdisintegrant is inappropriate for efavirenz's formulations." (Office Action, page 2, lines 6-7 from the bottom) Makooi does not expressly state that a low level of superdisintegrant is inappropriate, but Makooi's teachings, when considered as a whole, lead inescapably to the conclusion that Makooi teaches away from efavirenz formulations containing less than 10 wt.% superdisintegrant. In particular, Makooi emphasizes that very high levels of superdisintegrants are employed in its efavirenz formulations. In col. 3, lines 56-67, the reference teaches a process for manufacturing tablets or capsules using a "very high level" of a superdisintegrant in the wet granulation step, preferably about 20 to about 75 wt.% relative to the total dry weight of the materials used in the wet granulation step, and more preferably about 20 to about 55 wt.%. In col. 4, lines 56-61, the reference discloses that the wet granulation preferably contains 20 to 75 wt.% of sodium starch glycolate (a superdisintegrant), in contrast with the 1 to 10% that is used in typical wet granulations. Examples 1 and 2 in Makooi describe wet granulation capsule formulations containing 35.16 wt.% and 13.15 wt.% of superdisintegrant Na starch glycolate respectively, and Example 3 describes a wet granulation tablet formulation containing 20 wt.% Na starch glycolate. Clearly Makooi is directing the person of ordinary skill in the art to employ efavirenz formulations in which the superdisintegrant concentration is greater than 10% and is preferably 20% or more.

The Makooi disclosure does contain the statement in col. 3, lines 36-38 that superdisintegrants "generally are used at a low level in the solid dosage form, typically 1% to 10% by weight relative to the total weight of the dosage unit." Makooi is here making a comment on the state of the prior art. The nearly identical comment appears in Makooi's description of the prior art at col. 1, lines 54-57. The statement in col. 3 is <u>not</u> an embodiment of the invention being claimed by Makooi, and in fact contrasts sharply with Makooi's teaching that very high levels of superdisintegrant are required for solid dosage forms containing efavirenz. Makooi explicitly notes this contrast at col. 4, lines 56-61. Thus, the person of ordinary skill in the art would understand that, while superdisintegrants are generally used at a low level in solid pharmaceutical dosage forms, low levels are <u>not</u> suitable for dosage forms containing efavirenz. Considered as a whole then, Makooi clearly suggests to the skilled artisan that a low level of superdisintegrant in efavirenz formulations is inappropriate.

In arguing that Makooi does suggest the use of low levels of superdisintegrants in efavirenz formulations, the Examiner also asserted that "[i]n fact efavirenz capsules use just such amounts of superdisintegrants." (Office Action, page 2, lines 5-6 from the bottom) The

Examiner has provided no basis for this assertion. Makooi does not contain or support such a statement, as evidenced, for example, by Examples 1 and 2 of the reference which describe capsules containing more than 10 wt.% superdisintegrant. If the assertion is intended to be a reference to efavirenz capsules approved by the FDA and sold commercially under the tradename SUSTIVA®, it is misplaced, because SUSTIVA® capsules in fact contain more than 10 wt.% superdisintegrant and thus are embraced by the teachings of Makooi.

Remington and Christ, whether considered separately or together, do not cure the deficiencies in Makooi. Remington merely provides a general description of tablet preparation and tablet ingredients. It does not disclose efavirenz and does not teach or suggest efavirenz-containing tablet compositions. More particularly, Remington in no way contradicts Makooi's direction to the person of ordinary skill in the art to employ 10% or more superdisintegrant in efavirenz solid dosage forms. Christ teaches compounds that are structurally similar to efavirenz and provides a general description of dosages and formulations for these compounds (cols. 249-250). However, the reference expressly excludes efavirenz from its teachings via the proviso located in col. 4, lines 9-15. In fact, Christ discloses efavirenz to be prior art (see col. 2, lines 42-58) with respect to its invention. Accordingly, there is no motivation or suggestion to combine Christ with Makooi. Further, even if Christ and Makooi are combined, nothing in Christ contradicts Makooi's teaching that efavirenz solid dosage forms require 10% or more superdisintegrant.

In view of the foregoing remarks, it is clear that the combination of Makooi, Remington and Christ do not render the claimed invention prima facie obvious, and accordingly, contrary to the Examiner's position, evidence of unexpected results is not required to overcome the instant rejection. Nonetheless, assuming strictly for the sake of argument that the claims were prima facie obvious, reference is made to the evidence presented in the Rule 132 Declaration of Munir Alwan Hussain accompanying this communication (hereinafter the "Declaration"). The Declaration presents the results of several pharmacokinetic (PK) studies involving efavirenz tablets and capsules. These studies were bioequivalency studies that were part of the effort at DuPont Pharmaceutical Company (since acquired and now part of Bristol-Myers Squibb Pharma) to develop an efavirenz compressed tablet that was bioequivalent to the commercial capsule formulation of efavirenz.

Studies A and B in the Declaration were bioequivalency studies involving a comparison of tablets formulated in accordance with the teachings of Makooi to capsules having the commercial formulation. Study A compared the single-dose PK in fasted humans for 2 x 300 mg and 1 x 600 mg tablets containing 12 wt.% sodium starch glycolate (SSG) and 60 wt.% efavirenz to that of 3 x 200 mg commercial capsules (SUSTIVA® capsules, which contain 35 wt.% SSG and 39 wt.% efavirenz and which are manufactured in accordance with the teachings of Makooi). The results showed that the tablets were less bioavailable than the capsules; i.e, the tablets had

lower AUC and C_{max} values. Study B compared the single-dose PK in fasted beagle dogs for 2 x 300 mg tablets containing 10 wt.% and 20 wt.% SSG and 50 wt.% efavirenz to that of 3 x 200 mg capsules (Note: These capsules were not commercial capsules obtained from the factory, but they had the same composition and were prepared in the same manner -- i.e., in accordance with Makooi -- as commercial capsules.) The results showed that both the 10% and 20% SSG tablets were less bioavailable (i.e., had lower AUC and C_{max} values) than the capsules.

Studies C, D and E in the Declaration were bioequivalency studies involving commercial capsules and tablets of the instant invention. Study C compared the single-dose PK in fasted humans for 2 x 300 mg tablets containing 5 wt.% croscarmellose sodium (CROS) and 50 wt.% efavirenz to that of 3 x 200 mg commercial capsules. The results showed no significant differences between the PK obtained with the tablets versus the capsules. Study D compared the single-dose PK in fasted humans for 2 x 300 mg tablets and 1 x 600 mg tablets containing 5 wt.% CROS and 50 wt.% efavirenz to that of 3 x 200 mg commercial capsules. These results showed that the tablets had a higher bioavailability than the capsules; i.e., the tablets had AUC values equivalent to the capsules and higher C_{max} values than the capsules. Study E compared the single-dose PK in fasted humans for 2 x 300 mg tablets and 1 x 600 mg tablets containing 4 wt.% CROS and 50 wt.% efavirenz relative to that of 3 x 200 mg commercial capsules. These results demonstrated that the tablets had the same bioavailability as the capsules.

The conclusion from these studies is that the Makooi tablets of Studies A and B had less bioavailability than (and thus were not bioequivalent to) efavirenz commercial capsules, whereas the tablets of the claimed invention had the same (i.e., were bioequivalent to) or better bioavailability than the capsules. This result is neither taught nor suggested by Makooi in view of Remington and Christ.

Per the Declaration, it is also noted that, absent the development of a tablet bioequivalent to the commercial capsule, a full scale clinical trial with a non-bioequivalent tablet is required to demonstrate the tablet's safety and efficacy. Conducting a full scale clinical trial is costly in terms of time and resources and can also substantially delay approval and launch. The claimed invention resulted in the development of an FDA-approved bioequivalent tablet without the need for a full scale clinical trial, a benefit not achieved via the Makooi invention.

Clearly then, under the assumption that the claimed invention is prima facie obvious over the cited references (which it is not), the Declaration provides evidence of unexpected results rebutting the alleged prima facie case.

In view of the foregoing remarks, withdrawal of the section 103 rejection is requested.

The application is believed to be in condition for allowance and passage to issue is requested. The Examiner is invited to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

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